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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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			ART UNIT 1616	PAPER NUMBER
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/731,256	<b>Applicant(s)</b> MACDONALD ET AL.	
	<b>Examiner</b> Nathan W. Schlientz	<b>Art Unit</b> 1616	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 26 December 2006.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 28-61 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 28-61 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

The examiner for your application in the USPTO has changed. Examiner Nathan Schlientz can be reached at 571-272-9924.

### ***Status of Claims***

Claims 1-27 have been cancelled by amendment, filed 26 December 2006, and Claims 28-61 are new. Claims 28-61 have examined herein on the merits for patentability. No claim is allowed at this time.

### ***Claim Objections***

1. Claim 32 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. Claim 32 states, "the functional compound is adsorbed onto a surface of the nanoparticles." However, Claim 32 is dependent from Claim 28, which clearly states, "nanoparticles are bonded to a functional compound". Therefore, Claim 32 further broadens the scope of Claim 28 by changing the type of interaction between the nanoparticle and the functional compound.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 28, 30-38, 40 and 45 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 6,007,795 (hereinafter Masterman et al.).

Masterman et al. disclose a method for treating a bacterial infection by inhibiting bacteria in an oral and/or gastrointestinal cavity of a patient comprising: (a) providing a particle comprising: a degradable inorganic composite arranged on a surface of said particle; and a tetracycline antimicrobial agent adsorbed, or chemically bound, to said degradable inorganic composite, wherein said degradable inorganic composite is selected from alumina and silica wherein the preferred composite particles have a diameter of between 100 and 30,000 nm; (b) placing said particle into said oral and/or gastrointestinal cavity of said patient via a vehicle selected from a liquid (i.e., oral rinse/mouthwash) and a gel (i.e., toothpaste); and (c) exposing said particle to mechanical stresses (i.e., chewing, brushing and flossing), salivary enzymes, and gastrointestinal acidic pH, whereby said tetracycline antimicrobial agent (the molecular structure of which is illustrated hereinbelow) is desorbed from said degradable inorganic composite arranged on said surface of said particle, and thereby released into said oral and/or gastrointestinal cavity of said patient (abstract; column 1, lines 10-13 and 37-67; column 2, lines 1-13, 20, 27-31 and 41-54; column 3, lines 1-9 and 54-67; column 4,

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lines 64-67; column 5, lines 1-9 and 33-55). It is noted that Masterman et al. do not disclose the zeta potential of their particles. However, the zeta potential of Masterman et al. would inherently be the same as the instant claims, because the composite particles of Masterman et al. are made of the same material (tetracycline adsorbed or chemically bound to alumina).

Therefore, for the aforementioned reasons, Masterman et al. fully anticipate all the limitations of the instant claims.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
  2. Ascertaining the differences between the prior art and the claims at issue.
  3. Resolving the level of ordinary skill in the pertinent art.
  4. Considering objective evidence present in the application indicating obviousness or nonobviousness.
- 
1. Claims 28, 30-47 and 49-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Application Publication No. 2003/0082237 (hereinafter

Cha et al.) in view of The Merck Index, 10<sup>th</sup> Edition, p. 104, 408, 499, 1199 and 1200 [Monograph Nos. 739, 2815, 3435 and 8188] (1983) (hereinafter The Merck Index).

**Applicant claims:**

The Applicant claims a method of utilizing a triggerably releasable delivery system in the treatment of a patient comprising administering a plurality of nanoparticles containing alumina having a size of about 500 nm or less, wherein the nanoparticles are bonded to a functional compound comprising a moiety as shown in Claims 35 and 54 and possess a zeta potential of about 20 millivolts or more and the functional compound is released from the nanoparticles upon exposure to an environment or chemical condition.

**Determination of the scope and content of the prior art**  
**(MPEP 2141.01)**

Cha et al. teach a method for targeted delivery of a pharmaceutical agent and/or a nutraceutical to a site specific location (i.e., arterial, tumor, vagina, or gastrointestinal tract) within a patient comprising: (a) providing a microsphere delivery device comprising a shell substrate consisting of a plurality of inorganic metal oxide (i.e., aluminum oxide and silicon oxide) nanoparticles, the surface of which are functionalized by the attachment of a pharmaceutical agent (i.e., chemotherapeutic agents and fungicides) and/or a nutraceutical (i.e., dye); (b) placing said particle into said site specific location of said patient; and (c) exposing said particle to pH gradients and/or salt gradients, whereby said pharmaceutical agent and/or nutraceutical is thereby released into said artery, tumor, vagina or gastrointestinal tract of said patient (abstract;

[0004]; [0005]-[0010]; [0020]; [0021]; [0024]; [0025]; [0028]; [0040]-[0045]; [0055]; [0056]; [0060]-[0065]; [0078]; [0080]; [0089]; [0090]; [0093]; [0098]-[0102]; [0108]-[0111]; [0113]).

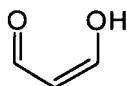
Cha et al. further teach that said pharmaceutical agent and said nutraceutical are released from said microsphere delivery device upon exposure to a pH below 6.5 or above 11 ([0099] and [0133]). Also, Cha et al. teach that the pH "window" for drug delivery can be adjusted and tuned by the use of modifications of the nanoparticles ([0133]). Cha et al. teach that if therapeutic agent delivery were applied to the vagina, the pH of the vaginal secretions (pH 3.5-4.5) would allow the opening of the microspheres and subsequent release of the drug contents ([0133]).

It is noted that Cha et al. do not disclose the zeta potential of their particles. However, the zeta potential of Cha et al. would inherently be the same as the instant claims, because the composite particles of Cha et al. are made of the same material (pharmaceutical agent bound to alumina).

#### **Ascertainment of the difference between the prior art and the claims**

##### **(MPEP 2141.02)**

Cha et al. does not explicitly teach that said pharmaceutical agent (i.e., chemotherapeutic agents and fungicides) and/or said nutraceutical (i.e., dye) comprises a chemical moiety (the molecular structure of which is illustrated hereinbelow), as claimed in Claims 35 and 54 of the instant application:



However, Cha et al. teaches a drug delivery system comprising a pharmaceutical agent (i.e., chemotherapeutic agent) and/or a nutraceutical (i.e., dye), such as Doxorubicin and Daunorubicin ([0010]). Furthermore, The Merck Index not only teaches that Doxorubicin and Daunorubicin are antineoplastic chemotherapeutic agents, but also teaches that Daunorubicin is a pH sensitive dye that changes color from pink at an acidic pH to blue at an alkaline pH.

### **Finding of *prima facie* obviousness**

#### **Rational and Motivation (MPEP 2142-43)**

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the instant application was filed to incorporate Doxorubicin and/or Daunorubicin as the pharmaceutical agent (i.e., chemotherapeutic agent) and/or nutraceutical (i.e., dye) taught in the method of Cha et al., since The Merck Index not only teaches that Doxorubicin and Daunorubicin are antineoplastic chemotherapeutic agents, but also teaches that Daunorubicin is a pH sensitive dye that changes color from pink at an acidic pH to blue at an alkaline pH. One of ordinary skill in the art at the time the instant application was filed would have been motivated to incorporate Doxorubicin and/or Daunorubicin as the pharmaceutical agent (i.e., chemotherapeutic agent) and/or nutraceutical (i.e., dye) taught in the method of Cha et al., because Cha et al. explicitly teaches incorporating chemotherapeutic agents and dyes, namely Doxorubicin and Daunorubicin, into drug delivery systems.

In addition, Cha et al. teaches a drug delivery system comprising a pharmaceutical agent, such as a fungicide. Furthermore, The Merck Index teaches



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utilizing Salicylanilide and Antimycin A<sub>1</sub> as fungicides. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the instant application was filed to incorporate Salicylanilide and/or Antimycin A<sub>1</sub> as the fungicide taught in Cha et al., since the Merck Index teaches that Salicylanilide and Antimycin A<sub>1</sub> are particularly useful as fungicides. One of ordinary skill in the art at the time the instant application was filed would have been motivated to incorporate Salicylanilide and/or Antimycin A<sub>1</sub> as the fungicides taught in Cha et al., since The Merck Index reasonably suggests utilizing Salicylanilide and Antimycin A<sub>1</sub> as fungicides. One of ordinary skill in the art at the time the instant application was filed would have had a reasonable expectation of success in incorporating Salicylanilide and/or Antimycin A<sub>1</sub> as the fungicides taught in Cha et al., since the Merck Index is the quintessential reference manual with respect to selecting specific organic chemical compounds based on their particularly disclosed therapeutic use.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

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2. Claims 29 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Masterman et al. in view of U.S. Patent No. 4,451,388 (hereinafter Payne).

**Applicant claims:**

The Applicant claims a method of utilizing a triggerably releasable delivery system in the treatment of a patient comprising administering a plurality of nanoparticles containing silica coated with alumina having a size of about 500 nm or less, wherein the nanoparticles are bonded to a functional compound and possess a zeta potential of about 20 millivolts or more and the functional compound is released from the nanoparticles upon exposure to an environment or chemical condition.

**Determination of the scope and content of the prior art**

**(MPEP 2141.01)**

The teachings of Masterman et al. are discussed above and incorporated herein by reference. In summary, Masterman et al. teach a degradable composite made of alumina or silica bound to an antimicrobial agent, wherein the degradable composite releases the antimicrobial agent upon exposure to either enzymes or mechanical stresses in the oral cavity. Masterman et al. further teach that the composite may also act as an abrasive if used in a toothpaste (column 3, lines 66-67).

**Ascertainment of the difference between the prior art and the claims**

**(MPEP 2141.02)**

Masterman et al. do not teach the nanoparticles comprising silica coated with alumina. However, nanoparticles of silica coated with alumina are well known for use in oral pharmaceuticals, as evidenced by Payne. Payne teaches a preparation of

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aluminum oxide coated silica sols that result in sols that are stable for a long period of time without any signs of gelation or other instabilities, such as precipitation (title; abstract; column 2, lines 60-65; and column 4, lines 43-48).

### **Finding of *prima facie* obviousness**

#### **Rational and Motivation (MPEP 2142-43)**

Therefore, it would have been *prima facie* obvious for one skilled in the art at the time of the invention to use nanoparticles of silica coated with alumina with a particle size of 100-30,000 nm as the nanoparticles of Masterman et al., because Payne teaches alumina coated silica sols have increased stability in comparison to silica sols.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

### ***Response to Arguments***

Applicant's arguments filed 26 December 2006 have been fully considered but they are not persuasive.

1. Rejection of Claims 1-7, 10, 14-17, 20, 24 and 26 under 35 USC 102(b) as being anticipated by Masterman et al.

The Applicants' argue on page 6 that Masterman et al. does not disclose nanoparticles having a size of about 500 nanometers or less, wherein the nanoparticles

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are bonded to a functional compound and possess a zeta potential of about 20 millivolts or more. The examiner respectfully disagrees. Masterman et al. disclose the anti-microbial agent may be attached to a skin composed of the degradable material (column 4, lines 64-67), wherein the preferred particle size is between 100 and 30,000 nm (column 5, lines 5-9). Masterman et al. do not disclose the zeta potential of their particles. However, the zeta potential of Masterman et al. would inherently be the same as the instant claims, because the composite particles of Masterman et al. are made of the same material (tetracycline adsorbed or chemically bound to alumina).

2. Rejection of Claims 1-8, 10-18, 20-24 and 26 under 35 USC 103(a) as being unpatentable over Cha et al. in view of The Merck Index.

The Applicants argue on page 7 that Cha et al. fails to disclose the use of nanoparticles that are bonded to a functional compound and possess a zeta potential of about 20 millivolts or more. The examiner respectfully disagrees. Cha et al. teaches that the nanoparticles may be functionalized with chemical links that incorporate a variety of therapeutic agents while still allowing their release (paragraph [0024]). With regard to the zeta potential, Cha et al. teach the nanoparticles made of silica or alumina and can be functionalized to provide a positive or negative charge (paragraph [0044]). Therefore, the nanoparticles of Cha et al., which have alumina on the exterior, would inherently possess the same zeta potential of the instant claims.

The Applicants further argue on page 7 that none of the cited references recognize the benefits achieved according to the present invention, such as the positive

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surface charge. The examiner respectfully disagrees. Masterman et al. disclose that the degradable material and the anti-microbial agent may have opposite ionic charges and the anti-microbial agent may be adsorbed onto the skin by ionic bonding (column 5, lines 1-4). Therefore, Masterman et al. clearly acknowledges the ionic surface charge and potential benefits associated with the charge. With respect to Cha et al., the prior art does not have to recognize a feature that is inherently a property of the composition. The surface charge of a particle is inherent to the particles composition, and is thus present in the particles of Cha et al.

### ***Conclusion***

Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.


### Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan W. Schlientz whose telephone number is 571-272-9924. The examiner can normally be reached on 8:30 AM to 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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